

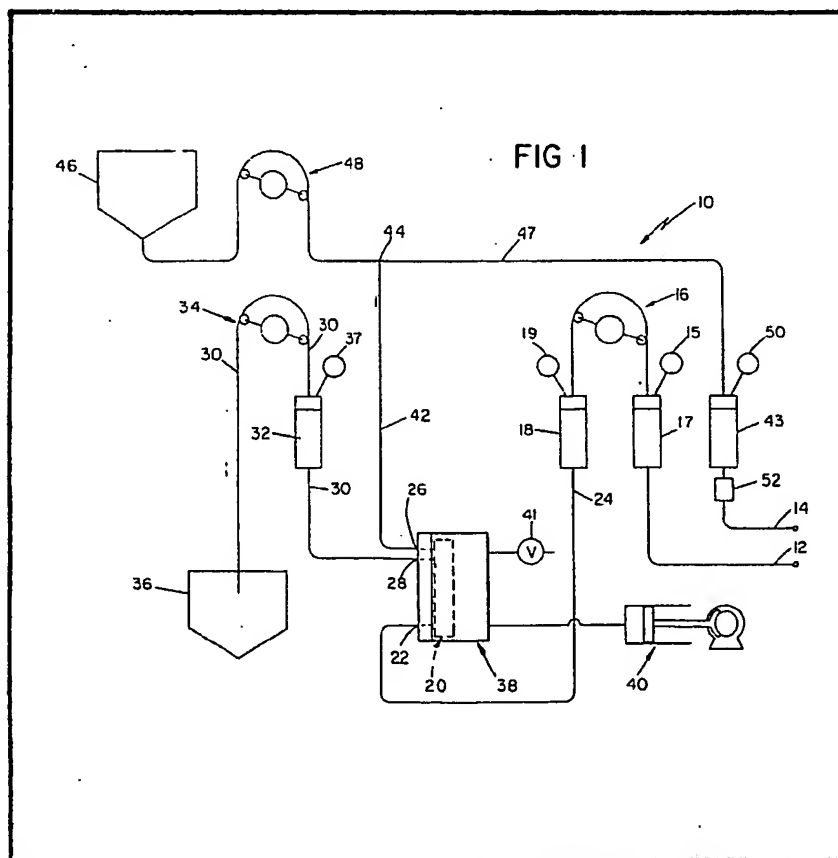
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(54) Plasmapheresis apparatus

(57) Apparatus for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of the particles such as blood, the apparatus including a housing having a particle mixture inlet port 22, a particle mixture outlet port 26, and a liquid filtrate outlet port 28. A microporous membrane is mounted within the housing to define a particle mixture flow channel and a filtrate channel, each channel being bounded on one side by opposite sides of said membrane, the particle mixture channel being in communication with the particle mixture inlet port and the particle mixture outlet port, the filtrate

channel being in communication with the filtrate outlet port. Means are provided to vary the geometry of the particle mixture channel or the filtrate channel to vary the relationships between two or more parameters such as the particle mixture flowrate, the flux through the membrane, the shear rate, the pressure gradient down the particle mixture flow channel, the pressure gradient down the filtrate channel, the particle concentration gradient, the transmembrane pressure, and the velocity profile of the particle mixture. A flow restriction may be provided in the filtrate channel to vary the changes in transmembrane pressure along the membrane. Replacement fluid may be introduced from a reservoir 46.



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FIG 2

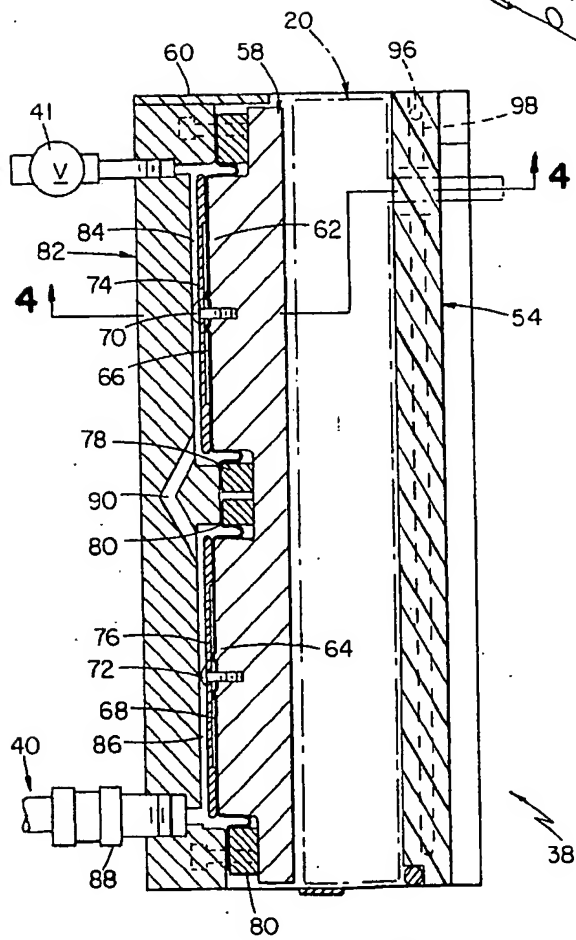
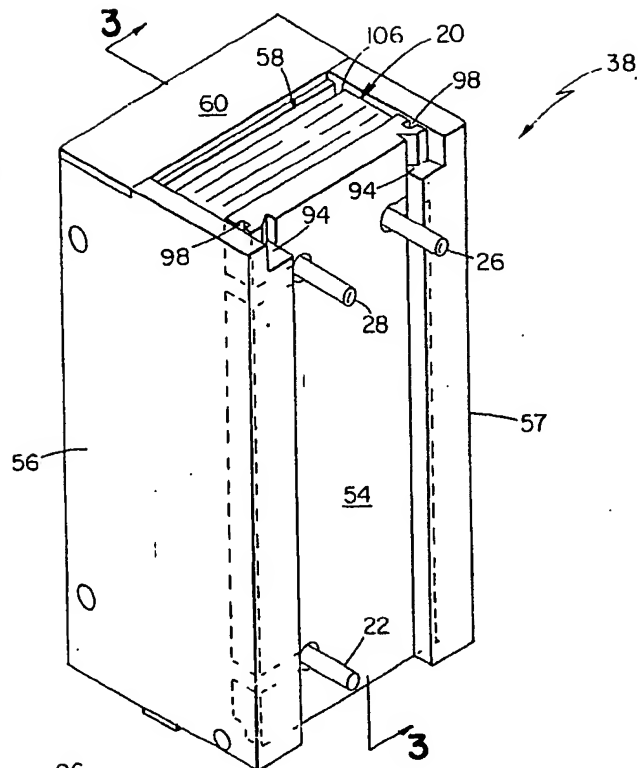


FIG 3

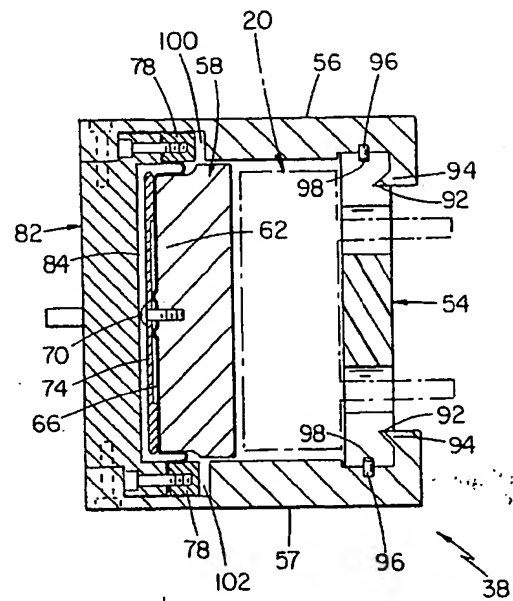


FIG 4

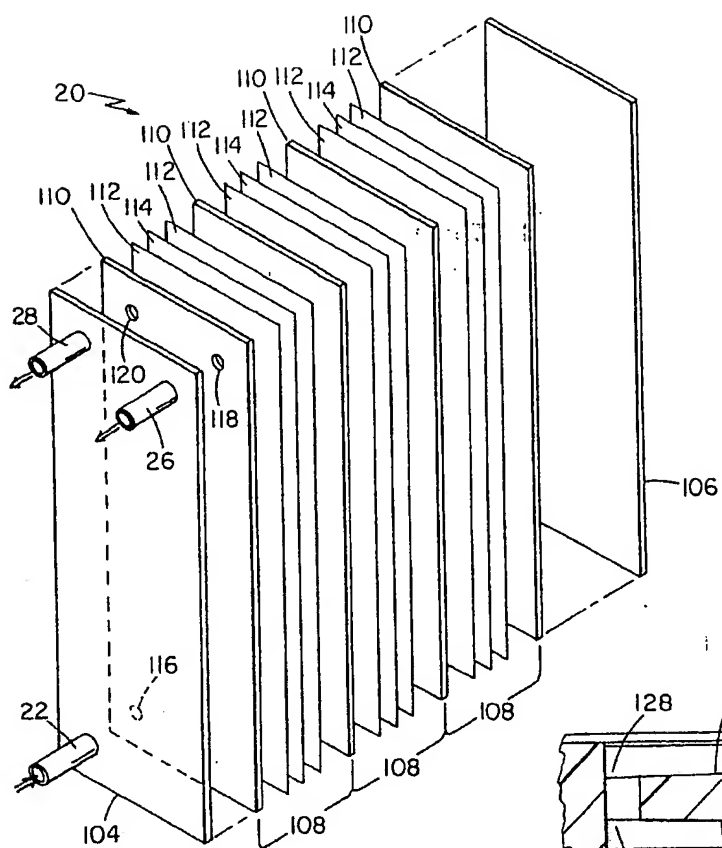


FIG 5

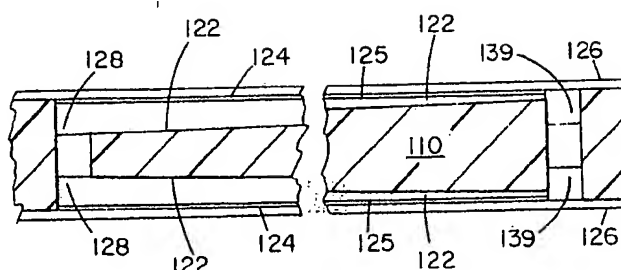


FIG 10

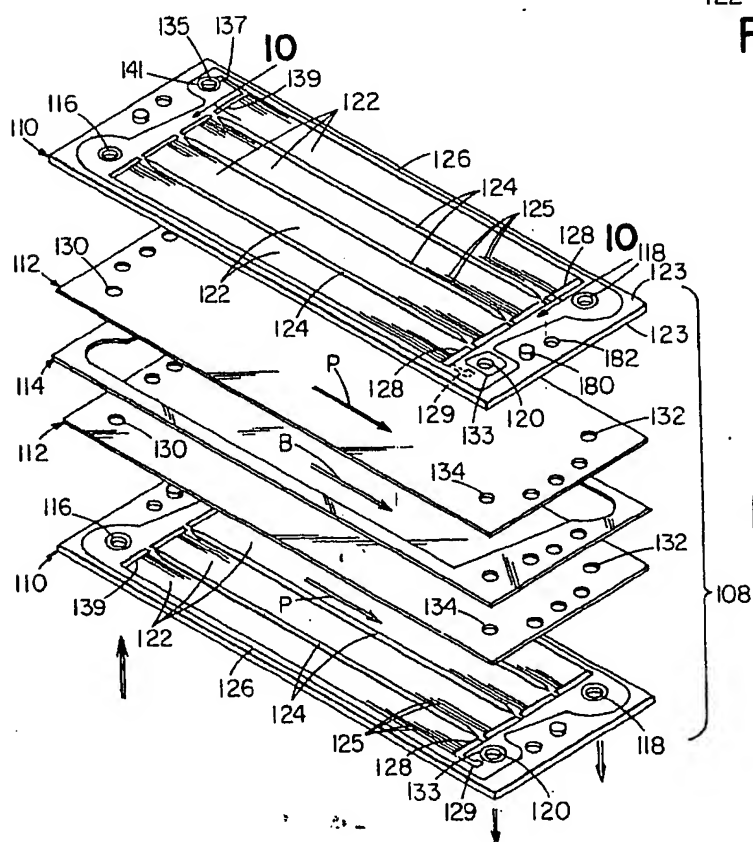


FIG 6

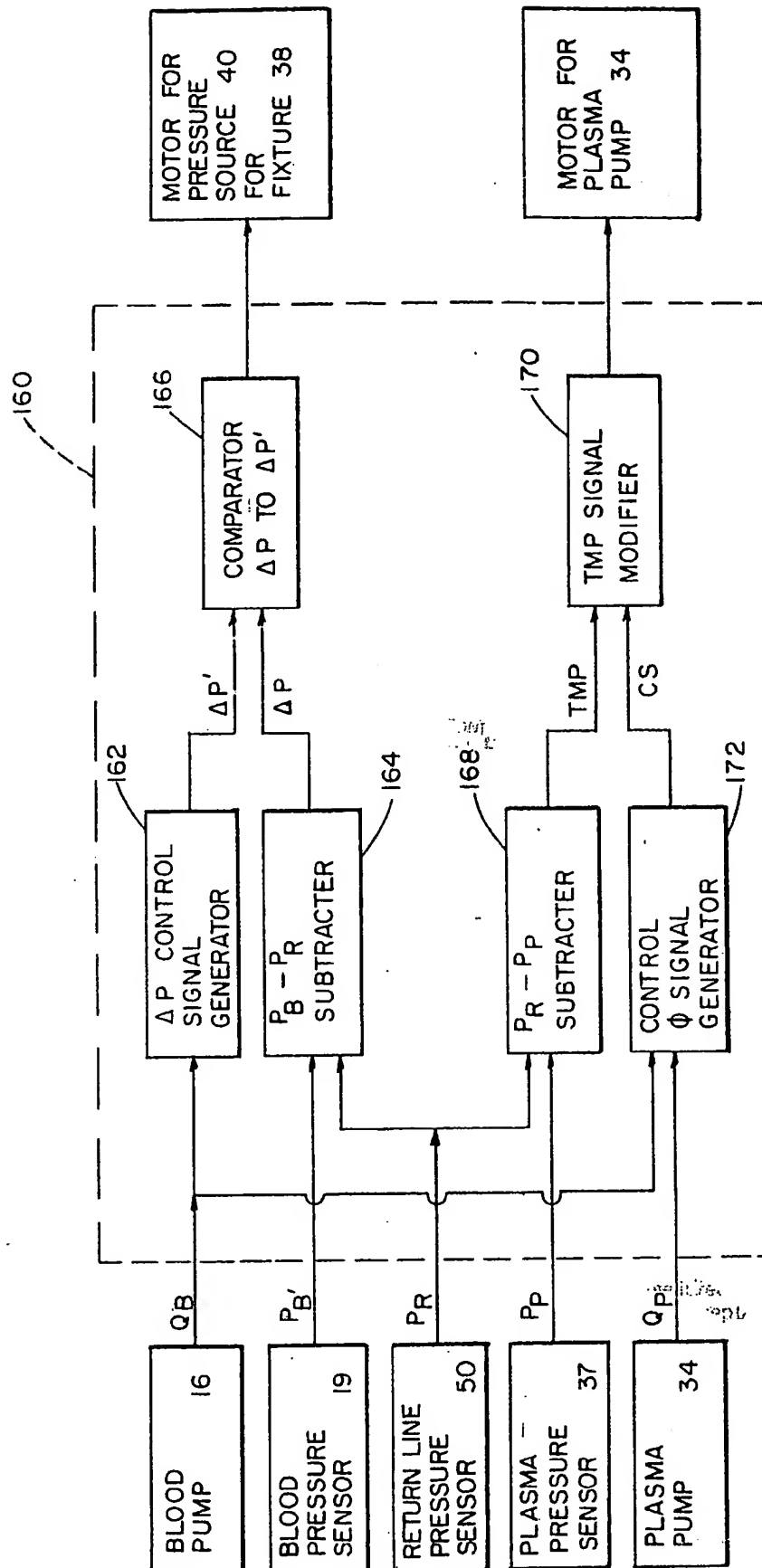


FIG 9

SPECIFICATION

Separating filtrates free of particles from liquid particle mixtures

Summary of the invention

5 It has been discovered that providing a microporous membrane filtration device with means to actively vary the geometry of either the particle mixture flow channel or the filtrate channel during operation provides increased versatility in varying
10 different control parameters in the device in response to the existing or desired operating conditions such as inlet flowrate, inlet particle concentration, and filtration rate, which operating conditions may vary with time or from one
15 application to another. For example, a desired flowrate for supplying the particle mixture to the device can be maintained, and the shear rate and other control parameters can be varied to optimize the flux to avoid clogging and particle
20 cell wall rupture simply by adjusting the height of the channel.

In preferred embodiments, the height of the particle mixture flow channel facing the membrane is varied by compressing the
25 membrane separating device; the membrane separating device is compressed in a fixture between a front plate and a piston plate that is slidably mounted along an axis transverse to the front plate, and pressure is applied to the rear of
30 the piston plate to vary the compression applied to the separating device; the front plate of the fixture has holes in it through which the ports for the membrane filtration device pass; the fixture includes a back plate behind the piston plate, and
35 the back plate is sealably connected to the piston plate by a diaphragm to define a pressure chamber between the back plate and the piston plate, and the back plate is fixably mounted with respect to the front plate so that increases in
40 pressure in the pressure chamber result in compressing the filtration device between the piston plate and the front plate; the geometry of the flow channel is varied in response to changes in a control parameter of the separating device;
45 the control parameter is the pressure drop in the particle mixture channel from the inlet to the outlet; means are included to detect the pressure drop in the particle mixture channel from the inlet to the outlet, to detect the flowrate of the particle
50 mixture into the separating device, and to maintain a proportional relationship between the pressure drop and the particle mixture flowrate by varying the height of the particle mixture channel; the proportional relationship between pressure
55 drop and the particle mixture flowrate is maintained so long as the pressure drop is below a predetermined level, and the pressure drop is maintained at the predetermined level for increases in the particle mixture flowrate above
60 that corresponding to the predetermined pressure drop level; the transmembrane pressure is maintained at a predetermined level by adjusting the rate of flow of the filtrate; the particle mixture inlet port is connected to an access line for a

65 patient, and the concentrated particle mixture leaving the device is returned to the patient with a replacement fluid; the particles are formed elements; and the filtrate is plasma.

In another aspect the invention features a
70 fixture for holding and compressing a membrane separating device with a particle mixture channel and a filtrate channel between a front plate and a piston slidably mounted along an axis transverse to the plates, the fixture also including pressure
75 means to vary the pressure on the back surface of the piston plate to vary the compression of the device and the geometry of a flow channel in the separating device. In preferred embodiments the front plate has holes in it through which ports of the separating device pass, and the fixture also
80 includes a back plate sealably connected to the back surface of the piston plate by diaphragm means to define a pressure chamber between the back plate and the piston plate.

In another aspect the invention features a separating device having a membrane mounted within housing means to define a particle mixture channel and a filtrate channel. The means
85 defining the filtrate channel provides a flow restriction in the filtrate channel so that there is a pressure drop along the filtrate flow path caused by the filtrate flow. This passively acts to reduce the changes in transmembrane pressure along the membrane, permitting the use of larger velocity
95 gradients in the particle mixture flow channel and thus higher flux along the membrane. In some preferred embodiments the flow restriction means includes means with V-shaped grooves facing the membrane to provide a V-shaped channels having
100 depths that are shallower at upstream portions than downstream portions; in other preferred embodiments the flow restriction means includes means providing a surface with roughness along the filtrate channel large enough to permit flow
105 between the surface and the membrane, but small enough to provide the desired pressure drop; in other preferred embodiments the flow restriction means is a flow obstructor placed in the filtrate channel (e.g., cloth or fibrous material);
110 there are pluralities of membranes, means to define filter channels, particle mixture flow channels, and filtrate channels, and the plurality of means to define filtrate channels are parallel plates; the housing means and microporous
115 membranes are adapted to cause variation in the geometry of particle mixture flow channels in response to the application of an external force to the housing; the variation in geometry is variation in height; and the housing means includes a shim in sealable contact with the microporous
120 membrane.

In another aspect the invention also features a separating device having a membrane mounted within housing means to define a particle mixture channel and a filtrate channel. When external
125 force is applied to the housing means, variation of the geometry of the particle mixture channel results. Also, the housing means and membrane provide particle mixture inlet and outlet manifolds

that are sufficiently large to have pressure drops associated with them that are small enough to permit determining the drop in pressure in the particle mixture flow channel by taking measurements in external lines connected to the ports. In preferred embodiments there are pluralities of membranes, means to define filtrate channels, filtrate channels and particle mixture flow channels, and the plurality of means to define filtrate channels are parallel plates; the housing means includes a shim in sealable contact with the microporous membrane; and the variation in geometry is variation in height.

In another aspect the invention features a separating device having a particle mixture channel and a filtrate channel defined by a membrane mounted between a port plate and an end plate. The peripheries of the plates are welded together, and the device is adapted to cause variation in the geometry of its particle mixture channels or its filtrate channels in response to the application of external force to the device. In preferred embodiments there are pluralities of plastic membrane support plates between the port plate and the end plate and pluralities of particle mixture channels, filtrate channels and membranes, and the peripheries of the plates are welded together; there are two membranes between each pair of membrane support plates; there is a shim to provide a seal with at least one membrane; and the device is adapted to cause variation in the height of the particle mixture channels in response to application of an external force to the port plate and the end plate.

In another aspect, the invention also features a separating device having a membrane mounted within housing means to define a particle mixture channel and a filtrate channel. The housing means includes an elastic shim in sealable contact with the membrane to cause a decrease in the height of one of the channels when the shim is compressed. In preferred embodiments there are pluralities of membranes, filtrate channels, and particle mixture channels, and the housing means includes a plurality of parallel plates; and the particle mixture channel is defined by a pair of membranes separated by the elastic shim.

In another aspect the invention features a separating device having a pair of microporous membranes mounted within housing means to define a particle mixture flow channel between the membranes and a pair of filtrate channels, each filtrate channel being bounded on one side by a membrane. By using two membranes to define the particle mixture channel, both large-area surfaces of the particle mixture flow channel are active in separating the filtrate. In a preferred embodiment, there are pluralities of membranes, filtrate channels, and particle mixture channels, and the housing means includes a plurality of parallel plates.

Description of the preferred embodiment

The structure and operation of the presently

preferred embodiment of the invention will now be described after first briefly describing the drawings.

Drawings

Fig. 1 is a schematic representation of blood cell separation apparatus according to the invention.

Fig. 2 is a perspective view of a separating device and a fixture of the Fig. 1 apparatus.

Fig. 3 is a vertical sectional view, taken at 3—3 of Fig. 2, of the Fig. 2 fixture.

Fig. 4 is a horizontal sectional view, taken at 4—4 of Fig. 3, of said fixture.

Fig. 5 is an exploded perspective view of said separating device.

Fig. 6 is an exploded perspective view of one set of channels of said separatory device.

Fig. 7 is a diagrammatic vertical sectional view of a portion of the Fig. 6 set of elements.

Fig. 8 is a diagrammatic vertical sectional view of a portion of the Fig. 6 set of elements when compression has been applied to the separating device.

Fig. 9 is a block diagram of control electronics for the Fig. 1 system.

Fig. 10 is a vertical sectional view, taken at 10—10 of Fig. 6, of an alternative embodiment of a plate element of the Fig. 5 separating device.

Structure

Referring to Fig. 1, there is shown plasma-pheresis apparatus 10 for separating plasma (small blood components including immunoglobulins, albumin and other proteins) from the "formed elements" (red blood cells, white blood cells and platelets) in a patient's blood and returning the formed elements to the patient with a makeup fluid. This process has utility in various applications, including therapeutically removing pathogenic substances contained in the plasma portion of a patient's blood. Apparatus 10 includes blood inflow line 12 and blood return line 14, for connection to lines attached to the patient. Line 12 has pressure sensor 15 and associated drip chamber 17 upstream of peristaltic blood pump 16 to monitor the blood pressure in the access line 12. Also connected to line 12 is a supply of anticoagulant (not shown). Downstream of pump 16 is blood inlet drip chamber 18 and its associated pressure sensor 19. Formed element separating device 20 has blood inlet port 22 (for receiving whole blood from the patient), blood outlet port 26, and plasma filtrate port 28. Blood inlet port 22 is connected by line 24 to the outlet of drip chamber 18. Plasma port 28 is connected by line 30 to plasma drip chamber 32, peristaltic plasma pump 34, and plasma collection bag 36. Plasma drip chamber 32 has pressure sensor 37 associated with it. Separator 20 is held within clamping fixture 38, described in detail below, which compresses device 20 to vary the height of the blood channels within it by means of pressure supplied by pressure source 40, which is a pressure chamber with a piston driven by a threaded rod connected to a control motor.

Device 38 has valve 41 for air bleeding. Blood outlet port 26 is connected by line 42 to junction 44, to which replacement fluid from replacement reservoir 46 is pumped by peristaltic pump 48.

5 Junction 44 is connected by line 47 to return drip chamber 43, having associated pressure sensor 50. The outlet of drip chamber 43 is connected to air bubble detector 52 and patient return line 14.

Referring to Fig. 2, separating device 20 is shown mounted within clamping fixture 38. Ports 22, 26, 28 extend through holes in front plate 54, which is vertically slidably mounted between side supports 56, 57. Device 20 is held against front plate 54 by piston plate 58 shown partially extending beyond cover plate 60.

Referring to Fig. 3, it is seen that piston plate 58 has circular piston projections 62, 64 extending from its rear surface. Rolling diaphragms 66, 68 are connected to the faces of piston projections 62, 64 by screws 70, 72 and circular retainers 74, 76, respectively. The peripheries of diaphragms 66, 68 are sealably sandwiched between bonnets 78, 80 and the inner surface of back plate 82. Back plate 82 has cylindrical depressions 84, 86 for receiving the two piston projections and their associated retainers. Female swivel connection 88, for connection to pressure source 40, communicates with depression 86, and air bleeding valve 41 communicates with depression 84. Channel 90 provides communication between depressions 84, 86.

Referring to Fig. 4, it is seen that front plate 54 has a pair of V-shaped grooves 92 for mating with V-shaped projections 94 extending rearwardly from transverse extensions of side supports 56, 57. Pins 96 extend inwardly from side supports 56, 57, and their unsupported ends are within vertical grooves 98, which run along the sides of front plate 54. Portions of bonnet 78, the periphery of diaphragm 66, and the associated periphery of back plate 82 are shown within recesses 100, 102 in side supports 56, 57.

Referring to Fig. 5, there is shown an exploded view of separating device 20. Blood inlet port 22, blood outlet port 26, and plasma outlet port 28 are formed on the front of plastic port plate 104. Between port plate 104 and end plate 106 are six sets 108 of plasma-blood-plasma channels (only three sets are shown in Fig. 5), each set 108 including two membrane support plates 110, two plastic, microporous membranes 112 (approximately 0.17 mm thick, and having an average pore size of 0.6 micron) and 0.004 inch thick polyethylene shim 114 between membranes 112. Adjacent plasma-blood-plasma channel sets 108 share a common membrane support plate 110. Referring to Fig. 6, the plates, membranes, and shim for one set 108 of the channels are shown. Blood channels B are provided between membranes 112, and plasma channels P are provided between membrane support plates 110 and membranes 112. Each membrane plate 110 is made of acrylonitrile butadiene styrene (ABS), and is approximately 0.114 inch thick, 8 3/4

inches long, and 3 1/4 inches wide. Holes 116 in plates 110 and holes 130 in membranes 112 are aligned with inlet port 22 to provide for the flow of incoming blood from inlet port 22 to all of blood channels B in channel sets 108. Holes 118 in plates 110 are similarly aligned with blood outlet port 26 and holes 132 in membranes 112 to provide for flow of the concentrated formed element mixture from blood channels B to outlet port 26. Holes 120 in plates 110 are aligned with plasma outlet port 28 and holes 134 in membranes 112 to provide for flow of plasma from plasma filtrate channels P to plasma outlet port 28.

On both the upper and lower surfaces of plates 110 are a plurality of elongated V-shaped grooves 122, which are separated by three parallel ribs 124. Around the perimeters of upper and lower surfaces 123 of plates 110, encompassing holes 116, 118, 120 and grooves 122, are continuous sealing beads 126, which each has a hemispherical cross-section of approximately 0.005 inch radius and extends above or below the planes of surfaces 123 of plate 110. As can be seen from Figs. 7 and 8, beads 126 on the upper and lower surfaces are not aligned with each other. Similar continuous sealing beads 133 surround holes 120 on plate 110. V-shaped grooves 122 are formed by surfaces making 45° angles with surface 123 and are approximately 0.04 inch wide and 0.02 inch deep. Tips 125 of plate portions between adjacent grooves 122 (Figs. 7 and 8) are approximately 0.003 inch above or below surfaces 123. The upper surfaces of ribs 124 are at the same level as surface 123. Grooves 122 end near plasma outlet port 120 at transverse plasma outlet channel 128, which collects plasma from the grooves and directs it to elbow channel 129, which passes under sealing beads 133 and communicates with the interior of plasma outlet hole 120 between outer surfaces 123. On the longitudinal ends of plate 110 are holes 180 and protuberances 182 for mating with corresponding protuberances and holes on adjacent plates to provide alignment during assembly.

When assembled, portions of membranes 112 surrounding holes 130 and 132 are heat-sealed to facing portions of plates 110 to provide inlet and outlet blood manifold seals and prevent leakage between the blood and plasma channels. Plates 110, membranes 112, and shims 114 are brought together. Sealing beads 126 provide a good seal between shims 114, membranes 112 and plates 110. The peripheries of the plates are welded together so that melted ABS from adjacent plates 110 mix together. As can be seen in Figs. 7 and 8, the edges of membranes 112 and shims 114 are inside the edges of plates 110. At the ends of the stack, melted plastic from port plate 104 and end plate 106 and the adjacent support plates 110 similarly mixes together, thus connecting and sealing the entire stack together to form device 20. Portions of membranes 112 surrounding holes 134 are squeezed by

continuous sealing beads 133 formed on the surfaces of plates 110 around holes 120 to provide plasma outlet channels isolated from blood outlet holes 118. Although holes 135, and sealing beads 141 (which are similar to holes 120, transverse channels 128, elbow channels 129, and sealing beads 133) are provided on the inlet side of plate 110 for ease of manufacture and assembly, there is no hole in port plate 104 corresponding to plasma port 128; thus, plasma collected in V-grooves 122 is directed to holes 120 communicating with plasma outlet port 28.

Port plate 104, end plate 106, membrane support plates 110 and shim 114 all act together as housing means to define the plasma and blood channels with microporous membrane 112.

A blood inlet manifold distributing blood from inlet ports 22 to channels B is provided by holes 116, membranes 112, holes 130, and the semi-circular and triangular depressions formed in the surfaces of plates 110 around holes 116. A blood outlet manifold is similarly provided by holes 118, membranes 112, holes 132 and the semicircular and triangular depressions formed in the surfaces of plates 110 around holes 118. Both of these manifolds are sufficiently large to cause pressure drops sufficiently smaller than the pressure drop along blood flow channels B to permit determination of the change in pressure along the blood flow channels based upon measurements of pressure in external lines connected to the blood inlet and outlet ports.

Operation

In operation, blood access line 12 and return line 14 are connected to the patient. Incoming blood travels through line 12, pump 16, and line 24 to inlet port 22 of separating device 20. Blood flows through holes 116 of plates 110 and holes 130 of membranes 112 and enters blood channels B between membranes 112. Because of the seals of portions of membranes 112 surrounding membrane holes 130 to facing portions of plates 110 surrounding holes 116, there is no flow of incoming blood to the plasma sides of membranes 112 facing plates 110, unless it passes through membranes 112.

Normally the pressure in blood channels B is higher than the pressure in plasma channels P on the other sides of membranes 112, and this causes membranes 112 to be forced against tips 125 of plates 110, thereby forming blood channels B. Components of the blood that are smaller than the pores of membranes 112 pass through membranes 112 and flow down the channels formed by V-grooves 122 and the facing surfaces of membranes 112 to transverse outlet channel 128, elbow channel 129, and plasma outlet holes 120 in plate 110. Because of the pressure seal between sealing beads 133 and portions of membrane 112 surrounding holes 134, there is no leakage between plasma channels P and blood channels B.

The formed elements, which are larger than the

pores of membrane 112, and other components which did not pass through membranes 112, flow to blood outlet holes 132 in membranes 112 and holes 118 in plates 110. Once again, the heat seals between portions of membranes 112 surrounding holes 132 and portions of plate 110 surrounding holes 118 prevent the leakage of formed elements into the plasma channels P. There is a gradual depression in plates 110 in portions surrounding holes 116, 118, and the blood pressure forces corresponding portions of membrane 112 against plates 110. Channels 128 are thin enough, and membranes 112 are rigid enough to prevent blockage of channels 128 by membranes 112 at the pressures used.

Referring to Fig. 1, the plasma filtrate from port 28 flows through line 30, drip chamber 32, and pump 34 to plasma collector reservoir 36. The concentrated formed element mixture from outlet port 26 flows through line 42 to junction 44 where flows through line 42 to junction 44, where replacement fluid from reservoir 46 is added. The makeup fluid from reservoir 46 is supplied to junction 44 by pump 48 at a controlled rate depending upon the particular patient and the setting of the control electronics for pump 48. For example, the makeup fluid could be pumped at a rate faster than plasma removal when it is desired to give the patient excess fluid to keep his blood pressure high to avoid problems associated with low blood pressure. The makeup fluid could also, in some instances, be pumped at a rate slower than plasma removal. The concentrated formed element mixture and makeup fluid flow through line 47, drip chamber 43, and air bubble sensor 52 to return line 14, and from there to the patient.

During plasmapheresis, pump 16 is operated to cause blood flow at a desired rate, often the maximum rate achievable without deleterious effects to the particular patient or collapsing of the blood vessel that blood is being removed from. The shear rate can then be maintained at a desired level (i.e., high enough to avoid pore clogging but low enough to avoid hemolysis) by adjusting the height between membranes 112 and blood channels B by controlling the compression applied to separating device 20 by fixture 38.

The following equation describes shear rate, SR, for fully developed flow of a Newtonian fluid in a rectangular channel where the width is sufficiently large in comparison to the height so that end effects can be neglected.

$$SR = \frac{6Q}{h^2w} = \left(\frac{Q_b}{w} \right)^{1/3} \left(\frac{\Delta P}{12\eta l} \right)^{2/3}$$

Where:

Q=flowrate of fluid in the rectangular channel,
w=width of the channel,
h=height of the channel,
l=length of the channel,
ΔP=pressure drop down the channel, and
η=viscosity of the fluid.

It is seen from the first equivalence presented by Equation (1) that the shear rate is directly proportional to the flow of blood and inversely proportional to the square of height H of the channel. The second equivalence presented in Equation (1) shows that the pressure drop down the channel is related to, and is therefore a measure of, the shear rate and the channel height.

Fig. 7 shows a channel B when the pressure from source 40 is low, and blood flow is relatively high. Fig. 8 shows the same channel when blood flow has decreased to a point that would require that blood channel height H be decreased to maintain the desired shear rate for the new conditions. This is done by increasing the pressure from source 40, which causes an increase in pressure between the back plate 82 and piston plate 58 and the moving of plate 58 to the right (Fig. 4), thereby compressing separating device 20 between plate 58 and front plate 54. Some of the compression is taken up by membranes 112, and some of the compression is taken up by shims 114 and plastic plates 110. Because membranes 112 are already supported by tips 125, changes in thickness of the device 20 result in changing height H between membranes 112. This change in device thickness and thus channel height is controlled by apparatus 10 by monitoring and controlling the pressure drop down blood channels B.

In Fig. 9, there is shown control electronics 160 for carrying out a particular protocol for operating apparatus 10. According to this protocol, height H is varied to result in a drop in pressure, ΔP , from blood inlet port 22 to blood outlet port 26 according to Equations (2) and (3):

$$\Delta P = [1.0 \text{ mm Hg/ml/min}] \times Q_B, \quad \text{for } 40 \leq Q_B \leq 100 \text{ ml/min} \quad (2)$$

$$\Delta P = 100 \text{ mm Hg}, \quad \text{for } (160 \geq Q_B \geq 100 \text{ ml/min}) \quad (3)$$

Where: Q_B is the total flow of blood into separating device 20.

The transmembrane pressure (TMP) near the outlet end of membranes 112 is maintained at 22 mm Hg, unless the plasma flow rate Q_p increase to 0.6 of Q_B while trying to achieve a TMP of 25 mm Hg. In that case, Q_p will be limited to 0.6 of Q_B . The value of 25 mm Hg has been selected as the outlet TMP because it results in a flux through membranes 112 that is acceptable at the same time the transmembrane pressure near the inlet is kept at or below 125 mm Hg, which is not high enough to cause hemolysis or clogging of the pores. (The pressure in plasma channels P remains substantially constant along their lengths).

In carrying out the above-described protocol, ΔP control signal generator 162 receives signals from blood pump 16 indicating total blood flow Q_B into device 20 and provides control signal $\Delta P'$, indicating the desired pressure drop through

blood channels B to comparator 166 according to Equations (2) and (3). Subtractor 164 receives signals from blood pressure sensor 19 indicating the pressure of the blood at inlet 22 of device 20 and signals from return pressure sensor 50 indicating the pressure of the concentrated formed element mixture leaving channels B at port 26 and provides a signal, ΔP , indicating the actual drop in pressure along channels B to comparator 166. If $\Delta P'$ equals ΔP , comparator 166 provides signals to the motor of pressure source 40 to maintain the pressure in fixture 38 at its present level to maintain heights H in the blood channels B at the present value.

If $\Delta P'$ exceeds ΔP by more than a predetermined value, comparator 166 sends signals to the motor for source 40 to increase the pressure in fixture 38 to decrease heights H so that the actual pressure drop, ΔP , will be increased to equal $\Delta P'$. If $\Delta P'$ is less than ΔP by more than a predetermined value, comparator 166 sends signals to the motor for source 40 to decrease the pressure in fixture 38 to result in increasing heights H in channels B. Pressure source 40 is monitored and controlled to prevent the pressure source 38 from exceeding safe pressure limits.

Subtractor 168 receives signals from return pressure sensor 50 indicating pressure in the concentrated formed element mixture leaving channels B at port 26 and signals from plasma pressure sensor 37 indicating the pressure of the plasma in device 20 and provides an output signal, TMP, indicating the actual transmembrane pressure near the outlet end of separating device 20. Control ϕ signal generator 172 (ϕ is defined as Q_p/Q_B) receives signals from blood pump 16 indicating the flow of blood into device 20, Q_B , and signals from plasma pump 34 indicating the flow of plasma, Q_p , through the membranes and out of device 20, and provides control signal CS to TMP signal modifier 170. As Q_p approaches 0.6 of Q_B , signal CS informs the TMP signal modifier 170, and TMP signal modifier 170 drives the plasma pump 34 so that Q_p does not exceed 0.6 Q_B . If Q_p does not approach 0.6 of Q_B , the TMP signal modifier drives the plasma pump 34 so that the desired TMP is achieved.

Other embodiments

Other embodiments of the invention are within the appended claims. For example, the formed element containing mixture need not be whole blood as in plasmapheresis as described above; it could be red blood cells, white blood cells, and/or platelets which have been separated from whole blood and frozen in an electrolyte solution. Similarly, the invention is not limited to separating formed elements, but also has application in separating bacteria or cultures of other cells (e.g., liver cells), which one wants to avoid destroying in the process of separating, and to separating precipitates or any other particles of

sizes greater than the pore size from liquid mixtures of the particles.

In addition to varying the height of channels, the channel geometry can be actively varied by varying the width (from Equation (1) it is seen that shear rate varies with both height and width for a rectangular channel) or the shape of the channels, e.g., one can compress the sides of a separating device to increase the channel height and decrease the channel width, or one can provide movable partitions to variably define the flow channels.

The geometry of the particle mixture channels (e.g., blood flow channels B) can be varied uniformly down the channels in response to other control protocols in addition to or in place of the maintenance of a proportional relationship between the pressure drop ΔP down the particle mixture channel and the flow of blood into the particle mixture channel described above. The other protocols can involve making control parameters of any of the following operating conditions: the pressure drop down the particle mixture channels, the pressure drop down the filtrate channels, the flow of particle mixture, the particle concentration, the transmembrane pressure, and the flux.

Also, the geometry of the channels can be actively or passively varied along their lengths to optimize the separation as a function of location along the membranes. This is desirable because the flowrates and particle concentrations are different at different points along the membranes, and, associated with these different flowrates and particle concentrations, are optimal transmembrane pressures, velocity profiles (perpendicular to the membrane), and particle concentration profiles (perpendicular to the membrane) for achieving the desired filtration rate while avoiding plugging and particle destruction. One way of achieving this optimization is actively varying the particle mixture channel geometry along the entire channel in response to such operating conditions as the flowrate of the particle mixture, the concentration of particles, the flux, the pressure drop in the particle mixture channel, the pressure drop in the filtrate channel, the transmembrane pressure profile along the membrane, the velocity profile in the particle mixture, and the concentration profile in the particle mixture. The operating conditions used become the control parameters for the protocols. Another way to effect at least some of the desired results is to passively vary the geometry of the filtrate channel to cause a desired pressure gradient in the filtrate channel, as is described in detail below. Also, one can actively vary the geometry of the filtrate channel in response to the operating conditions. (One way of varying the filtrate channel geometry is providing V-grooves by an accordion like member that can be expanded or contracted). Changes in the filtrate channel geometry cause changes in the filtrate pressure, in turn affecting the TMP, in turn affecting the operating conditions in the particle

mixture channel. Thus, the desired pressure gradient in the filtrate channel is the gradient which in conjunction with the pressure gradient in the particle mixture channel gives the preferred TMP and other operating conditions. These geometry changes in the particle mixture flow channel and the filtrate channel can be used together or independently.

By placing flow restriction means within the filtrate flow paths between the membranes and support plates, one can passively achieve pressure drops along the filtrate flow paths that approximate those along the blood channel flow paths, thereby permitting the use of higher velocity gradients in the particle mixture flow channel, thus permitting a high flux along the entire length of the membrane. This flow resistance can be provided by making the V-grooves shallower at the upstream end, where the flow is smaller, as is disclosed in Fig. 10. Flow resistance can also be provided by replacing the V-grooves with surface roughness of high enough magnitude to permit flow but of low enough magnitude to provide the desired pressure drop, or by placing flow obstructors, such as cloth or fibrous material, between the membranes and the membrane support plate. Also, the flow restriction can be such that, instead of providing a pressure drop approximating that in the blood channel flow path, one could provide a pressure drop to change the TMP along the membrane depending upon the concentration of formed elements or other operating conditions.

Also, the transmembrane pressure can be maintained by varying the flow of the particle mixture in addition to varying the filtrate pump, and can also be varied by varying the heights of the particle mixture channels. Other microporous membranes will work, and shims 114 can be avoided by providing for the desired blood channel depth by making tips 125 of V-grooves 122 lower in relation to surface 123.

Separating device 20 can contain any number of plasma-blood-plasma channel sets 108, or even just a plasma channel separated from a blood channel by a single membrane. If only a single plasma-blood-plasma channel set 108 is desired, membrane support plates 110 are not required; membrane supporting V-grooves 122 can be provided on the interior surfaces of port plate 104 and end plate 106, which can be welded together as adjacent plates 110 are shown welded together in Figs. 7 and 8.

In addition to compressing device 20 between front plate 54 and piston plate 58, device 20 could be secured to these plates, and a vacuum could be applied to depressions 84, 86 to expand device 20 to vary heights H of blood channels B.

The entire separating device need not be compressed, a bellows type device could be incorporated between port plate 104 and end plate 106 to compress the remainder of the housing means (i.e., shims 114, support plates 110 and membranes 112) to vary the heights of the particle mixture channels.

In place of the .004 inch thick polyethylene shim 114 one can use a thicker shim or one made of a more elastic material, e.g., rubber, or to provide a more compliant device to permit larger changes in the channel height H

Claims

1. Apparatus for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said apparatus comprising housing means having a particle mixture inlet port, a particle mixture outlet port, and a filtrate outlet port, a microporous membrane with pores of said predetermined size mounted within said housing means to define a particle mixture flow channel and a filtrate channel, each said channel being bounded on one side by opposite sides of said membrane, said particle mixture flow channel being in communication with said particle mixture inlet port and said particle mixture outlet port, said filtrate channel being in communication with said filtrate outlet port, and means to actively vary the geometry of said particle mixture flow channel or said filtrate flow channel during operation of said apparatus.

2. The apparatus of claim 1, wherein said means to vary is means to vary the height of said channel by compressing said housing means.

3. The apparatus of claim 2 wherein said means to compress is a fixture having a front plate with a first housing contacting surface, a piston plate having a second housing contacting surface and a pressure receiving surface, said piston plate being slidably mounted along an axis transverse to said first contacting surface, and

pressure means to vary the pressure acting on said pressure receiving surface, and wherein said housing is placed between said front plate and said piston plate, whereby varying the pressure on said pressure receiving surface varies the compression on said housing and varies said height.

4. The apparatus of claim 3 wherein said front plate has holes in it through which said particle mixture inlet port, said particle mixture outlet port, and said liquid filtrate outlet port pass.

5. The apparatus of claim 3 wherein said means to compress includes a back plate on the other side of said piston plate from said front plate, said back plate being sealably connected to said pressure receiving surface by diaphragm means to define a pressure chamber between said back plate and said pressure receiving surface, and wherein said back plate is fixedly mounted to prevent movement along said axis from said front plate.

6. The apparatus of claim 1 wherein said means to vary includes means to vary said geometry in response to changes in one or more control parameters.

7. The apparatus of claim 6 wherein said means to vary varies the height of said particle

mixture flow channel, and said control parameter is the pressure drop in said particle mixture channel from said inlet port to said particle mixture outlet port.

8. The apparatus of claim 7 wherein said means to vary include control means including means to detect the difference in pressure between said particle mixture inlet port and said particle mixture outlet port, means to detect the flowrate into said inlet port, and first comparator means to vary the height of said particle mixture channel to maintain a relationship between said difference in pressure and said mixture flowrate.

9. The apparatus of claim 8 wherein said relationship is proportional, and said first comparator means is adapted to maintain said relationship so long as said difference in pressure is below a predetermined level, and to maintain said difference at said predetermined level for increases in the particle mixture flowrate above that corresponding to said predetermined level.

10. The apparatus of claim 6, 7, 8 or 9 further comprising comparator means to maintain the difference in pressure of liquid in said particle mixture channel and pressure of liquid in said filtrate channel.

11. The apparatus of claim 6, 7, 8 or 9, further comprising a filtrate pump communicating with said filtrate outlet port, and comparator means to maintain the difference in pressure of liquid at said particle mixture outlet port and pressure of liquid at said filtrate outlet port at a predetermined level by adjusting the rate of flow of said filtrate pump.

12. The apparatus of claim 6 further comprising means to connect said particle mixture inlet port to an access line for a patient, a junction connected to said particle mixture outlet port, replacement fluid means for supplying replacement fluid to said junction, and a line connecting said junction to a return line for a patient.

13. The apparatus of claim 1, 6, 7, 8 or 9 wherein said particles are red blood cells, white blood cells, or platelets, and said pores in said microporous membranes are smaller in size than said particles.

14. The apparatus of claim 12 wherein said particles are formed elements, the pores in said microporous membranes are smaller in size than said formed elements, and said filtrate is plasma.

15. The apparatus of claim 1 wherein said means to vary is means to expand said housing means.

16. The apparatus of claim 1 wherein said geometry varies along the length of said channel.

17. The apparatus of claim 12 or 14 wherein said replacement fluid means includes means to supply said replacement fluid at a rate different from the rate of filtrate flow through said filtrate port.

18. A method for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said method comprising providing a separating device comprising

a housing means having a particle mixture inlet port, a particle mixture outlet port, and a filtrate outlet port, and

a microporous membrane mounted within said housing means to define a particle mixture flow channel and a filtrate channel, each said channel being bounded on one side by opposite sides of said membrane, said particle mixture channel being in communication with said particle mixture inlet port and said particle mixture outlet port, said filtrate channel being in communication with said filtrate outlet port;

supplying said liquid mixture of particles to said inlet,

maintaining the average pressure in said particle mixture channel above the average pressure in said filtrate channel, and varying the geometry of said particle mixture channel or said filtrate channel.

19. The method of claim 18, wherein said varying is accomplished by compressing said housing means.

20. The method of claim 19, wherein said compressing is accomplished by providing a fixture having a front plate with a first housing contacting surface, and a piston plate having a second housing contacting surface and a pressure receiving surface, said piston plate being slidably mounted on an axis transverse to said first contacting surface, and further comprising placing said housing means between said front plate and said piston plate, and varying the pressure acting on said pressure receiving surface to vary the compression on said housing means and to vary said geometry.

21. The method of claim 20, wherein said front plate has holes in it through which said particle mixture inlet port, said particle mixture outlet port, and said liquid filtrate outlet port pass.

23. The method of claim 20, wherein said fixture includes a back plate on the other side of said piston plate from said front plate, said back plate being sealably connected to said pressure receiving surface by diaphragm means to define a pressure chamber between said back plate and said pressure receiving surface, and wherein said back plate is fixedly mounted to prevent movement along said axis from said front plate.

23. The method of claim 18 wherein said geometry is varied in response to changes in one or more control parameters.

24. The method of claim 23 wherein said varying includes detecting the difference in pressure between said particle mixture inlet port and said particle mixture outlet port, detecting the flowrate into said inlet port, and varying the height of said particle mixture channel to maintain a relationship between said difference in pressure and said mixture flowrate.

25. The method of claim 24 wherein said

relationship is proportional, and said relationship is maintained so long as said difference in pressure is below a predetermined level, and said difference is maintained at said predetermined level for increases in the mixture flowrate above that corresponding to said predetermined level.

26. The method of claim 18, 23, 24 or 25 further comprising

providing a filtrate pump communicating with said liquid filtrate outlet port, and

maintaining the difference in pressure of liquid at said particle mixture outlet port and a pressure of liquid at said filtrate outlet port at a predetermined level, by adjusting the rate of flow of said filtrate pump.

27. The method of claim 23 further comprising connecting said particle mixture inlet port to an access line for a patient,

connecting said particle mixture outlet port to a junction also connected to a return line for a patient, and

supplying replacement fluid to said junction.

28. The method of claim 27 wherein said particle mixture is blood, said particles are formed elements, and said filtrate is plasma.

29. The method of claim 28 wherein said supplying is done at a rate different from the removal of filtrate by said filtrate pump.

30. The method of claim 18 wherein said varying is accomplished by expanding said housing means.

31. The method of claim 18 wherein said geometry varies along the length of said channel.

32. A fixture for holding and compressing a device for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said device comprising a housing means and a microporous membrane mounted within said housing means to define a particle mixture flow channel and a filtrate channel, said particle mixture flow channel being in communication with particle mixture inlet and outlet ports of said housing means, said filtrate channel being in communication with a filtrate outlet port of said housing means, said fixture comprising,

a front plate with a first housing means contacting surface,

a piston plate having a second housing means contacting surface and a pressure receiving surface,

said piston plate being slidably mounted along an axis transverse to said first contacting surface, and

pressure means to vary the pressure acting on said pressure receiving surface,

whereby said housing means can be placed between said front plate and said piston plate with said membrane being generally parallel to said front plate and said piston plate, and varying the pressure on said pressure receiving surface by said pressure means varies the compression on said housing means and varies the geometry of said particle mixture flow channel or said filtrate channel.

33. The fixture of claim 32 wherein said ports extend from a common face of said housing means, and said front plate has holes in it through which said ports pass.

5 34. The fixture of claim 32 or 33 wherein said means to compress includes a back plate on the other side of said piston plate from said front plate, said back plate being sealably connected to said pressure receiving surface by diaphragm
10 means to define a pressure chamber between said back plate and said pressure receiving surface, and wherein said back plate is fixedly mounted to prevent movement along said axis from said front plate.

15 35. A device for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said device comprising

20 housing means having a particle mixture inlet port, a particle mixture outlet port, and a filtrate outlet port,
a microporous membrane mounted within said housing means to define a particle mixture flow channel,

25 said particle mixture flow channel being in communication with said particle mixture inlet port and said particle mixture outlet port, and means to define a filtrate channel with said microporous membrane on the opposite side of
30 said membrane from said particle mixture flow channel and to provide flow restriction in said filtrate channel to cause a pressure drop along the filtrate flow path, to thereby passively vary the changes in the transmembrane pressure along
35 said membrane.

36. The device of claim 35, wherein said filtrate channel means includes means with V-shaped grooves facing membrane to provide V-shaped channels covered by said membrane, the
40 depths of said grooves being shallower at upstream portions than downstream portions to provide said pressure drop.

37. The device of claim 35, wherein said filtrate channel means includes means providing a
45 surface with roughness along said filtrate channel large enough to permit flow between said surface and said membrane but small enough to provide said pressure drop.

38. The device of claim 35 wherein a flow
50 obstruction is within said filtrate channel to provide said pressure drop.

39. The device of claim 38, wherein said flow obstruction is a piece of cloth material.

40. The device of claim 38, wherein said flow
55 obstruction is fibrous material.

41. The device of claim 35, wherein said housing means and said microporous membrane are adapted to cause variation in the geometry of said particle mixture flow channel in response to
60 the application of an external force to said housing means.

42. The device of claim 35 in which there are pluralities of membranes, means to define filtrate channels, filtrate channels, and particle mixture

65 flow channels, said plurality of means to define filtrate channels being a plurality of parallel plates.

43. A device for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said device
70 comprising

housing means having a particle mixture inlet manifold, a particle mixture outlet manifold, and a
filtrate outlet manifold, and

75 a microporous membrane mounted within said housing means to define a particle mixture flow channel and a filtrate channel, each said channel being bounded on one side by opposite sides of said membrane,

80 said particle mixture flow channel being in communication with said particle mixture inlet manifold and said particle mixture outlet manifold,

said filtrate channel being in communication with said filtrate outlet port,

85 said particle mixture inlet and outlet manifolds being sufficiently large to cause pressure drops sufficiently smaller than the pressure drop along said particle mixture flow channel to permit measurements of the change in pressure along
90 said particle mixture flow channel based upon measurements of pressure in external lines connected to said particle mixture manifolds,

said housing means and said microporous membrane being adapted to cause variation in the geometry of said particle mixture flow channel or
95 said filtrate channel in response to the application of an external force to said housing means.

44. The device of claim 43 in which there are pluralities of membranes, filtrate channels, and particle mixture channels, and said housing
100 means includes a plurality of parallel plates.

45. The device of claim 35 or 41, wherein said housing means includes a shim in sealable contact with said microporous membrane.

105 46. The device of claim 43 or 44, wherein said housing means includes a shim in sealable contact with each said microporous membrane.

47. The device of claim 41 or 43, wherein said variation in geometry is variation in height.

110 48. A device for separating a liquid filtrate free of particles larger than a predetermined size from a liquid mixture of said particles, said apparatus comprising a housing means including a port plate having a particle mixture inlet port, a particle
115 mixture outlet port, and a filtrate outlet port, and an end plate, and a microporous membrane mounted between said plates to define a particle mixture flow channel and filtrate channel with
120 said housing means, said particle mixture flow channel being in communication with said particle mixture inlet port and said particle mixture outlet port, said filtrate channel being in communication with said filtrate outlet port, the peripheries of said plates being welded together.

125 49. The device of claim 48 wherein said housing means includes a plurality of plastic membrane support plates between said port plate and said end plate, and there are a plurality of microporous membranes to define pluralities of

particle mixture flow channels and filtrate channels with said housing means, the peripheries of said membrane support plates, said port plate, and said end plate being welded together.

50. The device of claim 48 or 49, wherein each said particle mixture flow channel is defined by two membranes.

51. The device of claim 48 or 49, wherein there is a shim providing a continuous seal around the periphery of at least one said membrane.

52. The device of claim 48 or 49 in which said device is adapted to cause variation in the height of each said particle mixture channel or each said filtrate channel in response to application of an external force to said port plate and said end plate.

53. The device of claim 48 or 49 wherein said housing means includes means to provide a flow restriction in each said filtrate channel.

54. A device for separating a liquid filtrate free of particle larger than a predetermined size from a liquid mixture of said particles, said device comprising housing means having a particle mixture inlet port, a particle mixture outlet port, and a filtrate outlet port, and a microporous membrane mounted within said housing means to define a particle mixture flow channel and a filtrate channel, each said channel being bounded on one side by opposite sides of said membrane, said particle mixture flow channel being in communication with said particle mixture inlet port and said particle mixture outlet port, said filtrate channel being in communication with said filtrate outlet port, said housing means including an elastic shim in sealable contact with said microporous membrane to cause a decrease in the height of one of said channels when said shim is compressed.

55. The device of claim 54 in which there are pluralities of membranes, filtrate channels, and particle mixture channels, and said housing means includes a plurality of parallel plates.

56. The device of claim 54 or 55, wherein each said particle mixture channel is defined by a pair of membranes.

57. A device for separating a liquid filtrate free of particle larger than a predetermined size from a liquid mixture of said particles, said device comprising

housing means having a particle mixture inlet port, a particle mixture outlet port, and a filtrate outlet port, and

a pair of microporous membranes mounted with said housing means to define a particle mixture flow channel between said membranes and a pair of filtrate channels bounded on one side by said membranes,

said particle mixture flow channel being in communication with said particle mixture inlet port and said particle mixture outlet port,

said filtrate channels being in communication with said filtrate outlet port.

58. The device of claim 57 in which there are pluralities of pair of membranes, pairs of filtrate channels, and particle mixture channels, and said housing means includes a plurality of parallel plates.

59. The method of claim 23 wherein said varying includes varying the height of said particle mixture flow channel, and said control parameter is the pressure drop in said particle mixture channel from said inlet port to said particle mixture outlet port.

60. The method of claim 23, 59, 24 or 25 further comprising maintaining the difference in pressure of liquid in said particle mixture channel and pressure of liquid in said filtrate channel.

61. The apparatus of claim 23, 59, 24 or 25 wherein said particles are red blood cells, white blood cells, or platelets, and said pores in said microporous membrane are smaller in size than said particles.

62. The device of claim 48 or 49, wherein said device is adapted to cause variation in the geometry of said particle mixture flow channels or said filtrate channels in response to the application of an external force to the device.